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10/816,081	04/01/2004	David B. Rozema	Mirus.035.02.1	8619
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MIRUS CORPORATION 505 SOUTH ROSA RD MADISON, WI 53719			EXAMINER DUNSTON, JENNIFER ANN	
			ART UNIT	PAPER NUMBER
			1636	
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			05/31/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

**Application No.**

10/816,081

**Applicant(s)**

ROZEMA ET AL.

**Examiner**

Jennifer Dunston

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 19,22,23 and 27-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 19,22,23 and 27-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

This action is in response to the amendment, filed 3/9/2007, in which claims 1-18, 20-21 and 24-26 were canceled, and claims 19, 22, 23, 27, 29 and 30 were amended. Currently, claims 19, 22-23 and 27-32 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

### ***Election/Restrictions***

Applicant elected Group II without traverse in the reply filed on 9/18/2006. Currently, claims 19, 22-23 and 27-32 are under consideration.

### ***Response to Arguments - Double Patenting***

The rejection of claims 19 and 20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 9 and 10 of U.S. Patent No. 7,138,382 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claims 19 and 20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 9 of U.S. Patent No. 6,630,351 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claims 19 and 20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19, 21, 23, 25 and 26 of copending Application No.

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10/083,456 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

***Response to Arguments - 35 USC § 112***

Applicant's arguments, see pages 4-5, filed 3/9/2007, with respect to the rejection of claims 19-32 under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The previous rejection of claims 19-32 has been withdrawn.

***Response to Arguments - 35 USC § 102***

The rejection of claims 19, 20 and 24-28 under 35 U.S.C. 102(a) as being anticipated by Rozema et al (Bioconjugate Chem. Vol. 14, pages 51-57, published online 12/19/2002, cited on the IDS filed 2/8/2005) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claims 19, 20, 24 and 29 under 35 U.S.C. 102(a) as being anticipated by Murthy et al (Bioconjugate Chem. Vol. 14, pages 412-419, published online 1/15/2003, cited on the IDS filed 2/8/2005) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claims 19, 20, 24 and 29 under 35 U.S.C. 102(b) as being anticipated by Hoffman et al (WO 01/51092 A2, cited on the IDS filed 2/8/2005) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

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The rejection of claims 19, 20 and 24 under 35 U.S.C. 102(b) as being anticipated by Sullivan et al (US Patent Application Publication No. 2001/0044147 A1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claims 19-24 and 29-32 under 35 U.S.C. 102(b) as being anticipated by Schacht et al (US Patent No. 6,312,727 B1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claims 19, 20 and 24-29 under 35 U.S.C. 102(b) as being anticipated by Wolff (WO 00/75164 A1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/6/2007.

The rejection of claims 19, 20, 24-26 and 29 under 35 U.S.C. 102(e) as being anticipated by Wolff et al (US Patent No. 7,138,382 B2) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/6/2007.

The rejection of claims Claim 19, 20, 24-26 and 29 under 35 U.S.C. 102(e) as being anticipated by Monahan et al (US Patent No. 6,630,351 B1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/6/2007.

The rejection of claims 19, 20, 24-26 and 29 under 35 U.S.C. 102(e) as being anticipated by Monahan et al (US Patent Application Publication No. 2003/0199090 A1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/6/2007.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 22, 23 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1; see the entire reference). This is a new rejection, necessitated by the amendment of claim 19.

Wolff teaches a method for delivering a polynucleotide to the cytoplasm of a cell, comprising the steps of (i) condensing the polynucleotide with a cation to form a condensed polynucleotide binary complex (polycation/nucleic acid complex), (ii) associating the binary complex with a polyanion (polyanion/polycation/nucleic acid complex), and (iii) delivering the ternary complex to the cell where it is endocytosed (e.g., pages 16-19). Wolff teaches that the polyanion may be cleavable by the addition of a polyion cleavable in the side chain, where acids, esters and amides of carboxylic acid derivatives are reacted with amines (e.g., paragraph bridging pages 21-22). Specifically, Wolff teaches the reaction of dimethylmaleyl acid, a disubstituted maleic anhydride derivative, with an amine group on the polyion (e.g., paragraph bridging pages 11-12; paragraph bridging pages 21-22). Wolff teaches the reaction of the maleic

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anhydride derivative with the amine of the polymer to form a labile bond (e.g., paragraph bridging pages 21-22). The labile bond taught by Wolff et al is a pH-labile bond, as the specification teaches that the reaction of a maleic anhydride derivative with an amine results in the formation of a pH-labile bond (e.g., page 6, lines 14-15; Figure 2). Specific amines taught by Wolff et al are poly-L-lysine, spermine, spermidine, N,N'-bis(2-aminoethyl)-1,3-propanediamine (AEPD), and 3,3'-Diamino-N,N-dimethyldipropylammonium bromide (e.g., 6, lines 14-20; page 10, lines 13-19). Further, Wolff teaches that polyethylenimine (PEI, a polyamine) is capable of disrupting endosomal function without additional treatments. Moreover, Wolff teaches that agents that disrupt the endosome can be used to increase the delivery of the polynucleotide to certain parts of the cell (e.g., page 11, lines 18-21). Wolff teaches the formation of polymers containing two to more than 80 monomers, which would result in a molecular weight of at least 10,000 Daltons (e.g., paragraph bridging pages 6-7). Wolff teaches that the particles formed by the method are salt stable nanoparticles (e.g., Example 8; Table 3).

Wolff does not specifically teach the addition of dimethylmaleyl acid to polyethylenimine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide of Wolff to include the modification of polyethylenimine with dimethylmaleyl acid because Wolff teaches the reaction of dimethylmaleyl acid with amino groups and Wolff teaches it is within the skill of the art to use polyethylenimine in transfection methods. The addition of dimethylmaleyl acid to the polyethylenimine would result in the formation of a negatively charged reversibly inhibited

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membrane active polymer, which results in the formation of a ternary complex with a net negative charge.

One would have been motivated to make such a modification in order to receive the expected benefit of increasing delivery to the cells through disruption of the endosome as taught by Wolff. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1; see the entire reference) as applied to claims 19, 22, 23 and 29-32 above, and further in view of Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference).

The teachings of Wolff (WO 00/03694) are described above and applied as before.

Wolff (WO 00/03694) does not teach the method where the disubstituted maleic anhydride derivative is carboxydimethylmaleic anhydride.

Wolff (WO 00/75164) teaches the synthesis of 2-propionic-3-methylmaleic anhydride (carboxydimethylmaleic anhydride or C-DM) and the reaction of this compound to polyamines for use in the transfection of cells with a polynucleotide (e.g., page 19, lines 20-25; page 21, line 15 to page 22, line 30; page 23, lines 21-25; page 63, lines 1-18; page 65, lines 8-14; page 66, lines 21-27; Example 7). Wolff teaches that the addition of 2,3-dimethylmaleamic acid to a polyamine increases the transfection efficiency as compared to succinimic modified polyamine (e.g., page 78, Table). Wolff teaches that 2-propionic-3-methylmaleamic modified polyamine further increases transcription efficiency as compared to 2,3-dimethylmaleamic acid under the



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same conditions (e.g. page 78, Table). Wolff teaches that the bond between the maleic acid anhydride derivative and the polyamine is a pH-labile bond, which would be cleaved in the endosome (e.g., paragraph bridging pages 20-21; paragraph bridging pages 22-23; page 24, lines 5-17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transfection method of Wolff (WO 00/03694) to replace the dimethylmaleyl acid with the carboxydimethylmaleic anhydride taught by Wolff (WO 00/75164) because both references teach it is within the ordinary skill in the art to react a maleic acid anhydride derivative with a polyamine for use in transfection of cells with a polynucleotide.

One would have been motivated to make such a modification in order to receive the expected benefit of increased transfection efficiency as taught by Wolff (WO 00/75164). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

***Response to Arguments - 35 USC § 103***

The rejection of claim 25 under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (US Patent No. 6,312,727 B1) in view of Blattler et al (US Patent No. 4,569,789) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/9/2007.

The rejection of claim 25 under 35 U.S.C. 103(a) as being unpatentable over Sullivan et al (US Patent Application Publication No. 2001/0044147 A1) in view of Blattler et al (US Patent

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No. 4,569,789) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/6/2007.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.  
Examiner  
Art Unit 1636

/JD/

CELINE QIAN, PH.D.  
PRIMARY EXAMINER

